AMD070

Drug Class: **Entry and Fusion Inhibitors**

Drug Description

AMD070 is an investigational CXCR4 inhibitor. AMD070 is also known as AMD11070. [1]

HIV/AIDS-Related Uses

AMD070 is an investigational agent with in vitro activity against HIV-1. The safety, tolerability, and pharmacokinetics of AMD070 are being studied in clinical trials.[2]

Pharmacology

AMD070 prevents viral entry into cells by binding to the chemokine receptor CXCR4, the coreceptor used by T-cell tropic (X4), syncytium-inducing HIV viruses for membrane fusion and viral entry. AMD070 does not bind to CCR5, which mediates entry of macrophage-tropic (R5), nonsyncytium-inducing HIV viruses. The X4 strains are considerably more pathogenic; their appearance late in HIV infection correlates with CD4 count decline and rapid disease progression.[3]

AMD070 has not yet been fully evaluated in human trials. A small Phase I safety study of AMD070 in HIV uninfected male volunteers evaluated the safety, pharmacokinetic profile, and bioavailability of single and multiple doses of AMD070. Thirty subjects participated in this study. Single dose levels of 50, 100, 200, and 400 mg and multiple dose levels of 100, 200, and 400 mg twice a day (5 doses, with pharmacokinetic sampling performed following the last dose) were examined. Dose-dependent increases in peak plasma concentrations (Cmax) and the median area under the concentration-time curve (AUC) were observed following both single and multiple doses. Evidence of AMD070 accumulation was noted with repeated administration.[4] Food appears to have no effect on AMD070's absorption in humans.[5]

Most pharmacokinetic and toxicity data are from studies in rats and dogs. AMD070 is rapidly absorbed following oral administration. Oral bioavailability was calculated to be 20% in rats and 80% in dogs. Cmax was achieved 1 to 2 hours after administration of capsules, compared to less than 1 hour following administration of solution. The oral bioavailability of the capsule was 96% relative to the solution formulation. Bioavailability of AMD070 in dogs is significantly reduced when AMD070 is administered 30 minutes after feeding, compared to administration in the fasted state.[6]

Toxicokinetic tests were performed following single doses as a part of repeated-dose toxicity studies in rats and dogs in which AMD070 was administered twice daily. In the 28-day dog study, toxicokinetic determinations were performed at 5, 15, and 50 mg/kg body weight single-dose levels (10, 30, and 100 mg/kg/day dose groups). Dose-dependent increases in Cmax, generally increasing subproportionally to dose level, were observed in the dog study; this may be attributable to saturation of absorption pathways as administered dose levels increase. AUC and systemic exposure were generally proportional across the dose range; however, in a 28-day rat study, the kinetics of AMD070 were altered with repeated administration of the drug. Cmax and AUC increased from Day 1 to Day 28. Toxicokinetic determinations were performed at 31.25, 62.5, and 125 mg/kg body weight single dose levels (62.5, 125, and 250 mg/kg/day dose groups) in rats. Dose-dependent increases were generally noted for systemic exposure over the tested dose range. Further tests were performed as part of a single-dose maximum tolerated dose (MTD)/repeated-dose range-finding study in dogs following doses of 100 to 400 mg/kg. Dose-dependent increases in Cmax and AUC were not apparent across the dose range, and no evidence of accumulation of AMD070 was observed after 7 days of twice-daily administration at 200 mg/kg/day when administered as a solution or capsule. A delay in time to peak concentration (Tmax) was noted when AMD070 was administered in capsules versus in solution, but no other toxicokinetic differences were noted in comparing capsules and solution.[7]

Because no information concerning the reproductive toxicity of AMD070 is currently available, AMD070 is not being tested in women at this time, and male volunteers in AMD070 clinical

Pharmacology (cont.)

trials are advised to avoid participating in conception activities during AMD070 administration and for 2 weeks after stopping the drug.[8] AMD070 is not mutagenic in vitro; however, CXCR4 may play a role in hematopoiesis in utero.[9]

AMD070 is 84% to 97% protein bound at pharmacologically active concentrations; however, protein binding does not appear to have a significant effect in vitro. Limited information is available concerning the metabolism of AMD070. AMD070 represents the major circulating form of the drug in plasma; several putative metabolites have been noted in plasma samples from in vivo preclinical studies. Preliminary studies using cytochrome P450 (CYP450) isoform-specific chemical inhibitors and characterized human liver microsome preparations indicate that AMD070 may be a substrate for CYP3A4. AMD070 exhibited efflux-limited absorption in vitro in Caco-2 cells, indicating AMD070 may be a substrate for p-glycoprotein.[10]

AMD070 is eliminated from plasma in a biexponential manner with a terminal elimination half-life of approximately 6 to 10 hours in both the rat and dog.[11] In humans, AMD070 was eliminated in at least a biexponential manner with a terminal half-life of 10 to 20 hours.[12]

Adverse Events/Toxicity

Since AMD070 and AMD3100 are both CXCR4 inhibitors, the adverse events reported for AMD3100 may be similar to those for AMD070. In a study of 40 HIV infected people, AMD3100 was administered via a 10-day continuous infusion at up to 160 microg/kg/hour. The most common subjective complaints from study participants, regardless of whether they were attributed to study drug, included diarrhea (48%), flatulence (43%), headache (40%), nausea (35%), abdominal pain (33%), abdominal distension (25%), tachycardia (25%), dizziness (25%) and paresthesias (23%). Vital sign abnormalities, including hypertension (67%), hypotension (25%), and tachycardia (47%), were observed transiently in many participants, although there were no dose-related trends. A several-fold increase in white blood cells, CD4+ cell counts, and lymphocytes was seen in all participants but was of no clinical concern.[13]

In a small Phase I safety study of AMD070 in HIV uninfected volunteers, the drug was generally well tolerated; 3 of 12 participants complained of a transient mild to moderate headache after taking a single dose of AMD070 on an empty stomach.[14] No serious adverse events were reported, and adverse events were generally mild (mainly Grade 1 or 2). The most common adverse effects were pain, gastrointestinal disturbances, and Grade 1 tachycardia; other reported events included lightheadedness, palpitations, insomnia, shaky unsteady hands, feeling flushed, seasonal allergies, buzzing sensation, and heartburn.[15]

With short-term administration, there is a potential for acute gastrointestinal toxicity characterized by vomiting and diarrhea, usually within 1 to 2 hours of administration. These effects are expected to be transient. Bone marrow hypocellularity has been observed at the highest dose levels; reversibility of this effect has not been demonstrated. Lymphoid atrophy has been observed in the thymus, lymph nodes, and spleen. Heart rate elevations and blood pressure changes have also been noted.[16]

Drug and Food Interactions

In animal studies, the bioavailability of AMD070 was substantially reduced when the drug was administered 30 minutes after a meal. Current studies are investigating AMD070 when administered both on an empty stomach and with food.[17] In a small study of HIV uninfected volunteers, absorption of AMD070 did not appear to be affected by food.[18]

In vitro studies using five different CD4 T cell lines, CXCR-transfected cell lines, and PBMCs indicated AMD070 had additive or synergistic antiviral activity when evaluated in combination with other known HIV inhibitors, including fusion inhibitors (T-20), nucleoside reverse transcriptase inhibitors (zidovudine, tenofovir), and protease inhibitors (amprenavir).[19]

AMD070

Clinical Trials

For information on clinical trials that involve AMD070, visit the ClinicalTrials.gov web site at http://www.clinicaltrials.gov. In the Search box, enter: AMD070 AND HIV Infections.

Dosing Information

Mode of Delivery: Oral.[20]

Dosage Form: AMD070 has been studied in doses of 50, 100, 200, and 400 mg.[21]

Storage: Store at 2 C to 8 C (36 F to 46 F) and protect from moisture.[22]

Chemistry

Physical Description: Solid crystalline.[23]

Stability: After the bottle is opened, AMD070 capsules have a shelf-life of 28 days.[24]

Further Reading

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Manufacturer Information

AMD070
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Langley, BC Canada
604-530-1057

For More Information

Contact your doctor or an AIDSinfo Health Information Specialist:

• Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET

• Via Live Help: http://aidsinfo.nih.gov/live_help Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

References

1. Intl AIDS Conf - 15th, 2004. Abstract TuPeB4475.

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11. Protocol ID: ACTG A5210 - Ver. 2.0, p. 17

12. Protocol ID: ACTG A5210 - Ver. 2.0, p. 29

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14. Protocol ID: ACTG A5210 - Ver. 2.0, p. 29

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